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April 1982

Volume 12 Number 1

FDA Drug Bulletin

New Angina Drugs
Sucralfate Approved for Duodenal Ulcer
Ritodrine Update
Use of Approved Drugs for Unlabeled Indications
Hepatitis B Vaccine for Use in Selected Populations
Advice on Limiting Intake of Bonemeal
Bendectin PPI Available
Class I Recalls

New Angina Drugs

Two calcium channel blockers, nifedipine and verapamil, have been approved for treatment of vasospastic and classical effort-associated angina. These drugs are also referred to as "calcium entry blockers" or "calcium antagonists."

Drugs of this pharmacologic class have some common properties but also have important differences in clinical use.

Both agents inhibit transmembrane influx of extracellular calcium into cardiac and vascular smooth muscle, and produce, in isolated tissues, negative inotropic effects, depressed sino-atrial (SA) and atrio-ventricular (AV) node function, and vasodilation. At clinical doses in humans, however, the vascular effects are usually predominant, causing reduced peripheral vascular resistance and lower blood pressure and preventing or reversing coronary spasm. The effects on cardiac tissues are usually less prominent, probably because of afterload reduction and reflex sympathetic responses to vasodilation. In patients with normal cardiac function not on other negatively inotropic drugs, the negative inotropic effects of the drugs are not usually manifested.

In some cases, however, heart failure can be induced or worsened, and particular care must be paid to concomitant use of calcium channel blockers with beta blockers and to use in patients with aortic stenosis, where vasodilation would not be expected to produce significant afterload reduction.

Effects on AV and SA node function are also not prominent *in vivo* with nifedipine, although they can occur with verapamil.

Effectiveness

Verapamil, but not nifedipine, is an effective agent intravenously in interrupting supraventricular tachycardia and slowing the heart rate in atrial fibrillation.

Both drugs are effective in angina due to vasospasm and in chronic stable angina. Current labeling for nifedipine recommends it for use in stable angina only in patients "who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents." This reservation is based on the limited long-term evidence of safety and effective-

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FDA Drug Bulletin

Information of Importance To Physicians and Other Health Professionals

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ness in people with stable angina.

Although the effectiveness of these agents in angina is documented, many aspects of their effectiveness remain to be defined. Uncontrolled reports[1] and studies in which these agents have been added to, or substituted for, organic nitrates that had proved insufficiently effective[2,3] in vasospastic angina seem to indicate a special ability of the calcium antagonists to prevent vasospastic angina. In two well-controlled studies comparing nifedipine with isosorbide dinitrate, however,[4,5] there was little difference between the two treatments. There are no similar direct comparisons of verapamil and organic nitrates.

Safety

The side-effect profile of these agents overlaps but is by no means identical. In general, nifedipine appears to have a somewhat greater tendency to decrease peripheral resistance and lower blood pressure than verapamil, and does not tend to inhibit SA or AV nodal conduction. There is often a small increase in heart rate, and typical symptoms and signs of vasodilation (dizziness, flushing, numbness and tingling of extremities, peripheral edema, or palpitations) are common but usually tolerable.

More serious reactions can also occur. Excessive hypotension occurs occasionally with the use of nifedipine, usually during the initial titration or at the time of upward dosage adjustment. It may be more likely in patients taking beta blockers concomitantly.

A few patients have developed increased frequency, duration, or severity of angina upon starting nifedipine or at the time of dosage increases.[6]

Nifedipine dosage should be titrated over a 7 to 14 day period, if possible, to enable the physician to assess response at each dose level and monitor blood pressure before proceeding to higher doses.

There are isolated reports of patients recently withdrawn from beta blockers who have developed marked worsening of angina and even infarction.[7]

If possible, it is advisable to taper beta blockers before stopping them and beginning nifedipine. It does not appear that nifedipine can treat the increased angina sometimes associated with beta blocker withdrawal.

Concomitant use of nifedipine and beta blockers is usually well tolerated. However, there is little controlled experience with the combination, which is known to increase the likelihood of congestive heart failure and severe hypotension.

In rare instances, patients have developed heart failure after beginning nifedipine, usually when the drug was added to a beta blocker.[8] Patients with tight aortic stenosis may also be at greater risk of developing heart failure with nifedipine.[9]

Nifedipine may be given concomitantly with nitrates, but there have been no controlled studies to assess the antianginal effectiveness of this combination.

Nifedipine has been reported to increase serum digoxin concentrations by about 50 percent and must be used with great caution with concomitant digoxin.[10]

Blood pressure falls with oral verapamil, but marked decreases appear unusual. There is usually a slight decrease in heart rate. Symptoms of vasodilation are not common. On the other hand, verapamil can inhibit SA node function and AV conduction, and cause sinus bradycardia, nodal escape rhythm, and/or AV block. It is, therefore, contraindicated in patients with pre-existing AV conduction abnormalities or sick sinus syndrome.

Verapamil has generally been avoided in patients with pre-existing

heart failure and is contraindicated in patients with severe left ventricular dysfunction because it can worsen heart failure.

There are few studies of verapamil given in combination with beta blockers, but it is clear that the combination can impair cardiac function in some patients,[11] even when cardiac function was initially good.[12]

Verapamil can cause constipation, which is usually mild.

In studies carried out in the United States, there were two reported instances of rechallenge-confirmed liver injury among the first 1,000 patients treated.[13] The patients had a picture of predominantly hepatocellular injury (transaminases in the 1,000 unit range), although there were no liver biopsies to confirm this; there was prompt resolution on discontinuation of the drug. In nearly 4,000 patients treated since that time, only isolated instances of enzyme abnormalities have been reported. The world literature does not include any reports of liver injury similar to the one previously cited.[13]

Patients on verapamil should have periodic liver function tests. The drug should be stopped if abnormalities are seen. Physicians can help define the frequency and severity of this adverse reaction by reporting observed cases promptly to FDA.

In patients with impaired liver or kidney function, verapamil should be administered only with great caution. (Verapamil is highly metabolized by the liver and 70 percent of an administered dose is excreted as metabolites in the urine.)

Verapamil increases serum digoxin levels in patients on chronic digoxin therapy and must be used with caution in such patients. Maintenance digoxin doses should be reduced and the patient should be carefully monitored to avoid over- or under-digitalization when verapamil is administered.

Disopyramide should not be given within 48 hours before or 24 hours after verapamil due to the combined negative inotropic effects of the two drugs.

Until further data are available, verapamil and quinidine should be used together cautiously, especially in patients with hypertrophic cardiomyopathy, because there have been a few reports of pulmonary edema in patients given the combination.[14]

As with nifedipine, verapamil may be given concomitantly with nitrates, although the effectiveness of the combination has not been evaluated.

More complete information for prescribing these drugs is available in the package inserts.

References:

1. Antman E, et al.: Nifedipine therapy for coronary-artery spasm. *N Engl J Med* 1980; 302: 1269-1273.
2. Waters DD, et al.: Provocative testing with ergonovine to assess the efficacy of treatment with nifedipine, diltiazem, and verapamil in variant angina. *Am J Cardiol* 1981; 48:123-130.
3. Johnson SM, et al.: A controlled trial of verapamil for Prinzmetal's variant angina. *N Engl J Med* 1981; 304: 862-866.
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5. Ginsburg R, et al.: Randomized double-blind comparison of nifedipine and isosorbide dinitrate therapy in variant angina pectoris due to coronary artery spasm. *Am Heart J* 1982; 103:44-48.
6. Jariwalla AG, Anderson EG: Production of ischemic cardiac pain by nifedipine. *Brit Med J* 1978; 2:1181-1182.
7. Meinertz T, et al.: Beta blocker withdrawal syndrome. *Lancet* 1979; 1 (8110):270.
8. Robson RH, Vishwanath MC: Nifedipine and beta blockade as a cause of cardiac failure. *Brit Med J* 1982; 284:104.
9. Gillmer DJ, Kark P: Pulmonary edema precipitated by nifedipine. *Brit Med J* 1980; 284:1420-1421.
10. Belz GG, et al.: Digoxin plasma concentrations and nifedipine. *Lancet* 1981; 1:844.
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12. Chew C, et al.: Influence of severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. *Am J Cardiol* 1981; 47:917-922.
13. Brodsky SJ, et al.: Hepatotoxicity due to treatment with verapamil. *Annals of Int Med* 1981; 94(4):490-491.
14. Epstein S, Rosing D: Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. *Circ* 1981; 64:437-441.

Sucralfate Approved for Duodenal Ulcer

Sucralfate (Carafate), a basic aluminum salt of polysulfated sucrose, has been approved for short-term (up to 8 weeks) treatment of duodenal ulcer. The drug is chemically unlike any other drug used for treatment of duodenal ulcer.

Sucralfate exerts its effect through local rather than systemic action, and there is little systemic absorption. Although the mechanism of sucralfate's anti-ulcer activity has not been fully defined, studies suggest that, with extracellular protein, it forms an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. The medication has negligible acid-neutralizing capacity and its anti-ulcer effects cannot be attributed to neutralization of gastric acid.

In two U.S. multicenter, placebo-controlled studies with endoscopic evaluation at 2 and 4 weeks, sucralfate was more effective than placebo in promoting complete healing, and statistically significantly better at 4 weeks. In the first study, the ulcer healing rate at 4 weeks was 75.2 percent for sucralfate and 63.6 percent for placebo. In the second study the 4-week ulcer healing rate was 92 percent for sucralfate and 58 percent for placebo.

The better result in the second study may be attributable to the dosage schedule used. In the first trial, sucralfate was given 2 hours after meals and at bedtime rather than as now recommended, 1 hour before meals and at bedtime. The latter regimen was used in several foreign studies and in the second U.S. study.

There are no known contraindications to the use of sucralfate. Adverse reactions in clinical trials involving more than 2,400 patients were minor and only rarely led to the discontinuation of the drug. The most frequent complaint was constipation, which was reported by 2.2 percent of patients. Other adverse effects reported in no

more than 1 of every 350 patients were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

No long-term studies have been carried out and there is no recognized reason for long-term use of sucralfate. Specifically, it is not known whether sucralfate can prevent ulcer recurrence. Long-term studies will be needed to assess the possibility of adverse effects associated with long-term use, e.g., effects on absorption of fat-soluble vitamins.

The recommended adult dosage is 1 g four times a day on an empty stomach. Antacids may be prescribed as needed for relief of pain but should not be taken within 30 minutes before or after administration of sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been confirmed by X-ray or endoscopy.

Ritodrine Update

Since the approval of ritodrine (Yutopar) for use in premature labor (see November 1980 and July 1981 *Drug Bulletins*), FDA has been monitoring several areas of concern about the drug's known cardiovascular effects. In light of a number of adverse reaction reports, the labeling of ritodrine has been updated to warn about:

- the need to monitor the patient's state of hydration;
- the possibility of pulmonary edema with or without the concomitant use of corticosteroids, many cases of which seem to be related to overhydration;
- the possible unmasking of occult cardiac disease, the first sign of which may be chest pain.

Ritodrine, a beta$_2$-sympathomimetic drug, may be useful in preterm labor in pregnancies of at least 20 weeks gestation when contraindications have been ruled out.

However, in pregnancies of more than 32 weeks, physicians should carefully weigh the risks and benefits before administering the drug.

When gestational age is in doubt, intrauterine growth retardation should be considered in the differential diagnosis of preterm labor. Among low birth weight infants, about 9 percent may be growth retarded for gestational age. Prolongation of labor beyond term will not correct the growth retardation of these babies.

Initial administration of ritodrine is intravenous. To minimize the risk of hypotension, the patient should be maintained in the left lateral position during infusion and careful attention should be given to her state of hydration. The amount of i.v. fluids administered should be monitored to avoid either circulatory fluid overload (overhydration) or inadequate hydration. An excess sodium load should be avoided in hydrating the patient.[1]

The boxed warning for ritodrine has been amended to read:

> Maternal pulmonary edema has been reported in patients treated with Yutopar, sometimes after delivery. While occurring infrequently, it has occurred more often when patients were treated concomitantly with corticosteroids. Maternal death from this condition has been reported with or without corticosteroids given concomitantly with drugs of this class.
>
> Patients so treated must be closely monitored in the hospital. The patient's state of hydration should be carefully monitored. (See Dosage and Administration.) If pulmonary edema develops during administration, the drug should be discontinued. Edema should be managed by conventional means.
>
> Because cardiovascular responses are common and more pronounced during intravenous administration of Yutopar, cardiovascular effects, including maternal pulse rate and blood pressure and fetal heart rate, should be closely monitored. Observe for premonitory or actual maternal signs and symptoms of pulmonary edema. A persistent high tachycardia (over 140 beats per minute) and/or persistent tachypnea (respiratory rate over 20 per minute) may be signs of impending pulmonary edema with drugs of this class.
>
> Occult cardiac disease may be unmasked with the use of Yutopar. If the patient complains of chest pain or tightness of chest, the drug should be temporarily discontinued and an ECG should be done as soon as possible.
>
> The drug should not be administered to patients with mild to moderate preeclampsia, hypertension, or diabetes unless the attending physician considers that the benefits clearly outweigh the risks.

Reference:
1. Philipsen T, et al.: Pulmonary edema following ritodrine-saline infusion in premature labor. *Ob Gyn* 1981; 58(3): 304-7.

Use of Approved Drugs for Unlabeled Indications

The appropriateness or the legality of prescribing approved drugs for uses not included in their official labeling is sometimes a cause of concern and confusion among practitioners.

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and which FDA has approved. These are commonly referred to as "approved uses." This means that adequate and well-controlled clinical trials have documented these uses, and the results of the trials have been reviewed and approved by FDA.

The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term "unapproved uses" is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

With respect to its role in medical practice, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects the data on safety and effectiveness on which drug approval is based.

Hepatitis B Vaccine for Use in Selected Populations

An inactivated hepatitis B vaccine (Heptavax-B) has been licensed for use in the United States. It is intended for selected populations at high risk of acquiring hepatitis B, one of three known forms of viral hepatitis. (The others are hepatitis A and non-A non-B hepatitis.)

The vaccine is the first to be made from human blood. Noninfectious antigen is purified from the plasma of asymptomatic human carriers of hepatitis B. After a series of chemical treatments, followed by the addition of alum adjuvant, the vaccine is administered in three intramuscular injections over a 6-month period.

Vaccination is not intended for the general population, but is recommended for persons older than 3 months of age who are at increased risk of hepatitis B virus infection. These persons will include health care workers, institutionalized patients, laboratory workers, hemodialysis staff and patients, family contacts of carriers, some military personnel, and persons with numerous sexual partners.

There continues to be a dialogue among government agencies, industry, and the medical community about use of the vaccine in selected high-risk groups. The Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control (CDC), with assistance from representatives of FDA, the National Institutes of Health, and the medical community, has met several times to discuss specifically which population groups should receive this vaccine. The ACIP will meet once more in May of this year to draft final guidelines for use of this vaccine.

Efficacy

In clinical trials, 85 to 96 percent of persons receiving three doses of either 20 mg or 40 mg of vaccine were immune to infection. The duration of protection is presently unknown. However, in clinical trials, vaccine-induced antibodies, shown to provide protection against infection, persisted for at least 24 months in those receiving all three doses and will probably last for at least 5 years. After this time, a booster may be necessary to maintain immunity.

Side effects have been mainly local, mild, and transitory.

Availability

Due to the complexity of the methods used for producing the vaccine, it will be summer or fall of 1982 before the product is generally available from Merck, Sharp & Dohme. This manufacturer can supply complete physician information.

Advice on Limiting Intake of Bonemeal

Due to the unknown but often substantial lead content of individual samples of bonemeal and dolomite, FDA advises practitioners that these substances should be used as little as possible in infants, young children, and pregnant or lactating women.

Bonemeal is used primarily as calcium and/or phosphorus supplements. Bonemeal supplements are usually composed of finely crushed, processed bone and are packaged in powder, capsule, tablet, or wafer form. The source of bone is usually cattle but sometimes also horses. Bone marrow may also be added to this product. All bonemeal products contain lead which originates primarily from the diet of the animals from which the bone is taken. Bone serves as a repository for lead in the body and, in general, the older the animal the more lead in its bones.

Dolomite is a mineral deposit, consisting of calcium-magnesium carbonate with traces of other elements, including lead. Dolomite is used as a calcium and magnesium supplement and, like bonemeal, may be purchased in powder, capsule, tablet, or wafer form.

While a large portion of the small amounts of dietary lead ingested by humans is excreted, some is deposited in the mineral fabric of bone and some goes into soft tissue. Infants and children tend to absorb lead more efficiently than adults. When it is consumed in excess, lead may produce toxic reactions including central nervous system damage, anemia, and abdominal pain. As in animals, the accumulation of lead in human bone increases with age. Additionally, studies with

adult volunteers have shown that over a long time, the accumulation of lead in the body is proportional to the level of intake.

FDA Surveys

FDA has undertaken limited surveys to identify the extent of lead contamination of bonemeal and to determine whether the problem is limited or industry-wide.

One survey by FDA's Division of Consumer Studies of approximately 3,000 persons, 16 years of age and older, determined that about 1 percent of the population surveyed consumed bonemeal as a calcium source. More than 90 percent of the individuals consuming bonemeal were women, 50 years of age or older. The available information suggests that the average intake of bonemeal does not usually exceed 10 g/day.

No reliable information is available on the use of bonemeal as a calcium source for young children or infants. However, it is possible that bonemeal has been used as a calcium supplement for infants who have an intolerance for milk.

Although levels are usually lower, FDA scientists have found some samples of bonemeal containing lead at concentrations as high as 17 to 20 parts per million (ppm). Comparably high levels of lead have also been detected in some samples of dolomite.

It is known that the consumption of bonemeal containing 5 to 10 ppm lead by infants and children may result in lead intakes that clearly exceed the FDA recommended tolerable or maximal daily intake from all sources. For the infant, lead intake should be as low as possible and less than 100 micrograms/day, and for children between 6 months and 2 years the intake of lead should be no more than 150 micrograms/day.

Special Risk

Individuals at special risk of lead toxicity from the consumption of bonemeal or dolomite include infants, children, women of childbearing age, and possibly the elderly. Others who ingest bonemeal at the recommended doses (usually not more than 5 to 10 grams/person/day) would not ordinarily exceed the WHO/FAO (World Health Organization/Food and Agriculture Organization) guideline for a tolerable daily adult intake of 430 micrograms of lead. However, individuals who consume more than two to three times the recommended dose would be at greater risk if the lead content of the bonemeal is high.

Pregnant or lactating women taking bonemeal or dolomite to meet increased calcium needs may have sufficient increased lead intake and absorption to present a health hazard to the developing fetus, via placental transfer of lead, or to the nursing infant from its mother's milk.

Bendectin PPI Available

A patient package insert (PPI) for Bendectin, an antiemetic combination of doxylamine and vitamin B_6 used in pregnancy, has been issued by the manufacturer, Merrell Dow Pharmaceuticals.

Pads of the PPIs are being distributed to retail pharmacies and physicians who are high prescribers of the drug, and are available to other health professionals from the manufacturer, upon request.

A Spanish language version of the PPI will be available upon request from the manufacturer.

In its summary section, the PPI explains: "Bendectin is used to treat the nausea and vomiting that may occur during the first few weeks of pregnancy. You should take this drug only if nausea and vomiting interfere with your eating or daily activities and if other treatments prescribed by your doctor do not relieve your symptoms. These other treatments include eating soda crackers or dry toast, or drinking hot or cold liquids as soon as you wake up in the morning.

"There is no way to prove that any substance taken by pregnant women does not cause birth defects on rare occasions. For this reason, no drug, including Bendectin, should be taken during pregnancy unless it is clearly necessary."

As was discussed in the March 1981 issue of the *Drug Bulletin*, the revised physician labeling for Bendectin cautions physicians that the drug should be used only when more conservative treatment for nausea and vomiting in pregnancy has failed and when symptoms are sufficiently distressing to require drug intervention.

Class I Recalls

As a special service to health professionals, the *Drug Bulletin* is publishing information on recent Class I recalls. The following products have been withdrawn voluntarily in firm-initiated Class I recalls because they pose serious health hazards:

Infant Formula

Nursoy Concentrated Liquid, 13-ounce cans, coded A26M, B2M, and B9M, and Nursoy Ready-to-Feed 32-ounce cans coded A28M and B11M. Codes may be preceded by a number such as 1,2, or 3, which can be ignored. Example: 2A26M. Formula lacks vitamin B_6, which can result in serious health effects ranging from irritability to convulsions. Cans may be returned to the retailer for refund or replacement. Recall date: March 3, 1982.

SMA powder and liquid with code numbers A25M through A31M, and B1M through B15M. Code numbers may be preceded by a number such as 1,2, or 3, which can be ignored. Example: 2A25M. Formula is deficient in vitamin B_6, which can result in serious health effects ranging from irritability to convulsions. Cans may be returned to the retailer for refund or replacement. Recall date: March 12, 1982.

Defibrillator

Safeguard 3, serial numbers 290, 374, 379, 380, 1001, 1002, 1006. The storage capacitor may fail, resulting in low discharge energy and consequent failure to defibrillate. The manufacturer, Safeguard Medical Systems, Inc., Beltsville, Md., will replace faulty condensors. Recall date: Dec. 14, 1981.

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Use a separate report form for each case. Additional pages may be attached.

I. PATIENT/REACTION INFORMATION (ITEMS 1-12)

Items 2, 3, 4, 5. In case of a congenital malformation, record age, weight and height of the *mother*, and sex of the *baby*.

Item 8. Describe signs, symptoms and course of the drug related event.

Item 9. Indicate the status of the patient as of the reporting date and include discharge summary and/or autopsy findings, if available.

Item 10. Describe all diagnostic tests and exams results done as result of events in Item 8. Pertinent base line values and laboratory normals should be included.

Item 11. If "yes", describe treatment in Item 8.

Item 12. Hospitalization Required: If "yes", describe treatment in Item 8.

II. SUSPECT DRUG INFORMATION (ITEMS 13-20)

Item 13. Trade name and lot number, when available.

Item 14. As of date in Item 7. If drug(s) was given in a different dose or form previously, include dates and total daily dose for each drug exposure.

Item 15. As of the date in Item 7.

III. RECENT/CONCOMITANT DRUGS AND MEDICAL PROBLEMS (ITEMS 21-22)

Item 22. When reporting a congenital malformation, include date of mother's last menstrual period, gravidity, parity and previous abortions.

IV. OTHER INFORMATION (ITEMS 23-26)

Item 24. If this is a follow-up to a previous report, attach copy of initial report.

Item 25. (Record the name, title and address of the provider originating the report. THIS INFORMATION IS KEPT IN CONFIDENCE BY THE FDA AND IS NOT RELEASED UNDER THE FREEDOM OF INFORMATION ACT.)

After completing the form on the other side of this sheet, please tear off the page, triple fold, and staple or seal with tape. No postage is necessary.

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DRUG EXPERIENCE REPORT

FORM APPROVED; OMB 0910-0004.
Use of this form is prohibited after 12/31/85.

FDA CONTROL NO.
ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS (In Confidence)	2. AGE	3. SEX	4. WGT.	5. HT.	6. REPORTING DATE MO	DA	YR	7. REACTION ONSET DATE MO	DA	YR

8. DESCRIBE SUSPECTED REACTION(S)

9. OUTCOME OF REACTION TO DATE
- ☐ Alive with sequelae
- ☐ Recovered
- ☐ Still under treatment for reaction
- ☐ Died (Give cause/date)

10. TESTS/LABORATORY DATA CONFIRMING REACTION (Include biopsy and/or autopsy results)

11. WAS OUTPATIENT TREATMENT FOR REACTION REQUIRED? ☐ Yes ☐ No

12. WAS HOSPITAL TREATMENT FOR REACTION REQUIRED? ☐ Yes ☐ No

II. SUSPECT DRUG(S) INFORMATION

13. SUSPECT DRUG(S) - TRADE/GENERIC NAME(S), MANUFACTURER, IND/NDA NO.

14. TOTAL DAILY DOSE

15. ROUTE OF ADMINISTRATION

16. INDICATION(S) FOR USE

17. THERAPY DATES *(From/To)*

18. THERAPY DURATION

19a. WAS TREATMENT WITH SUSPECTED DRUG REDUCED IN DOSAGE? ☐ Yes ☐ No OR: ☐ Discontinued

19b. DID REACTION ABATE? ☐ Yes ☐ No

20a. WAS DRUG REINTRODUCED OR DOSE INCREASED? ☐ Yes ☐ No

20b. DID REACTION REAPPEAR? ☐ Yes ☐ No

III. RECENT/CONCOMITANT DRUGS AND MEDICAL PROBLEMS

21. OTHER DRUGS	TOTAL DAILY DOSE	ROUTE	DATES/DURATION OF ADMINISTRATION	INDICATIONS

22. DESCRIBE OTHER RELEVANT MEDICAL HISTORY (i.e., allergies, environmental or occupational exposure, previous drug reactions, pregnancy with gravidity/parity, ethnic origin.)

Your cooperation is needed to insure comprehensive, accurate, and timely use and interpretation of these data.

23. MFR NAME/ADDRESS

MFR CONTROL NO.

DATE SENT TO FDA

24. Check one
- ☐ Initial Report
- ☐ Follow-up Report

25. REPORTER'S NAME AND ADDRESS (In confidence)

NOTE: *Required of manufacturers by 21 CFR 310.300, 310.301 and 431.60. Manufacturers may attach additional clinical material and product analyses at their discretion.*

26. MAY THE SOURCE OF THIS REPORT BE RELEASED TO THE ARMED FORCES INSTITUTE OF PATHOLOGY? ☐ Yes ☐ No

FORM FDA 1639 (4/81) PREVIOUS EDITIONS ARE OBSOLETE.

12/2

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Volume 12 Number 2

FDA Drug Bulletin

Salicylate Labeling May Change Because of Reye Syndrome

Benzyl Alcohol May Be Toxic to Newborns

Hepatotoxic Potential of Ketoconazole Under Investigation

Inappropriate Use of Smallpox Vaccine

Oral Medication for Cystic Acne

Implantable Drug Pump

Approval of PUVA for Severe Psoriasis

Erythromycin Estolate To Remain on Market

Class I Recalls

Salicylate Labeling May Change Because of Reye Syndrome

FDA is evaluating possible changes in the labeling for products containing aspirin or other salicylates because of the association of salicylates with Reye syndrome (RS) in children.

First recognized about 19 years ago, RS is a rare, acute, life-threatening encephalopathy occurring mostly in children under 16 years of age who are recovering from viral infections, particularly influenza and varicella. It is characterized by vomiting and lethargy, which may progress to delirium, coma, and death.

The U.S. Centers for Disease Control (CDC) estimates that 600 to 1,200 cases of RS occur each year in the United States. The disease is fatal in 20 to 30 percent of all cases, and permanent brain damage results in other cases.

An association between RS and ingestion of various medications has been suspected for some time (see November 1976 *Drug Bulletin*). However, it was not until the results of recent case-control studies were available that an assessment of the possible association with specific drugs could be made.

Earlier this year, CDC reported on four studies (one each from Arizona and Ohio and two from Michigan). In these studies the use of salicylates and salicylate-containing drugs during the antecedent viral illness was more common in patients who developed Reye syndrome than in matched controls.

On the basis of these reports and upon recommendations of an advisory panel, in the Feb. 12, 1981, issue of its *Morbidity and Mortality Weekly Report*, CDC stated: "The exact pathogenesis of this disease and the possible role of salicylates in its pathogenesis remain to be determined. Additional well-controlled studies are also needed. Until definitive information is available, CDC advises physicians and parents of the possible increased risk of Reye syndrome associated with the use of salicylates for children with chickenpox or influenza-like illnesses."

The American Academy of Pediatrics' Committee on Infectious Diseases

HE 20. 4003/3:

FDA Drug Bulletin

Information of Importance
To Physicians and
Other Health Professionals

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reviewed the data in these studies and issued a statement in the June 1982 issue of *Pediatrics*, advising that the use of salicylates should be avoided in children suffering from influenza or varicella.

The committee recommended "that consideration should be given to the advisability of using any antipyretic medications for these illnesses."

Because of a number of criticisms of the conduct of these studies and the interpretation of the data, FDA undertook an independent analysis of the matter. This analysis included: (1) a review of materials available from the investigators in Arizona, Michigan, and Ohio; (2) a review of summaries provided by CDC on studies concerning RS and salicylates; (3) a review of analyses by employees and consultants of manufacturers of salicylate drug products and consumer representatives; (4) site visits to the Michigan and Ohio state health departments to obtain further details on how these studies were conducted and to audit data on case records; and (5) a review of a subset of the data from the Ohio study containing day-by-day information on disease symptoms and drug use.

In the course of the review, questions were raised about study design; however, these were not considered sufficient to change substantially the interpretation of the data. The FDA analysis generally supported the association between salicylates and RS shown in the earlier evaluations of the data.

The studies performed are not able to demonstrate conclusively whether the association is causal, but the accumulated evidence is sufficiently strong to justify the FDA's advisory caution on the use of salicylates in children with those viral illnesses particularly associated with the development of RS.

FDA presented its analyses at an open public meeting on May 24, 1982, which it sponsored jointly with CDC and the National Institutes of Health (NIH). At the completion of the meeting, the majority of the scientific experts believed that the new analyses supported the earlier evidence suggesting an association between use of salicylates and the development of RS.

Aspirin and other salicylates are found in single ingredient products or in combination with other medicines; labels of over-the-counter drug products contain a list of ingredients. Aspirin remains a medically useful drug with anti-inflammatory actions not found in other over-the-counter antipyretics.

Benzyl Alcohol May Be Toxic to Newborns

Solutions containing benzyl alcohol or other preservatives should not be used in newborns to flush intravascular catheters. Solutions for diluting or reconstituting medications for newborns also should contain no benzyl alcohol or other preservatives.

FDA has received reports of 16 fatalities in newborns weighing less than 2,500 grams in whom bacteriostatic sodium chloride for injection containing 0.9 percent benzyl alcohol had been used for flushing intravenous catheters.[1,2] Some of the infants received additional benzyl alcohol when bacteriostatic water was used to dilute or reconstitute medications.

The deaths were preceded by a syndrome consisting of metabolic acidosis, central nervous system depression, respiratory distress progressing to gasping respirations, hypotension, renal failure and sometimes seizures and intracranial hemorrhages. Blood and urine samples of affected infants revealed high levels of benzyl alcohol, benzoic acid or its metabolite, hippuric acid.

Toxicity from benzyl alcohol appears to have been caused by large daily doses of benzyl alcohol per kilogram of body weight; daily intake in these cases ranged from 99-404 mg/kg/day. Each mililiter of 0.9 percent solution contains 9.0 mg of benzyl alcohol.

In the two medical centers reporting the 16 cases, no additional cases of the toxic syndrome were seen after solutions containing benzyl alcohol were eliminated.[1,2] There have been no reports of toxicity in older infants, children, and adults.

On May 28, FDA sent letters to pediatricians, hospital pharmacists, and hospital administrators, recommending that solutions used to flush intravascular catheters or for diluting or reconstituting medications in newborns not contain benzyl alcohol or any other preservative. Sterile sodium chloride for injection (not bacteriostatic sodium chloride for injection) should be used for flushing intravenous catheters.

The agency is working on labeling changes with the manufacturers and the U.S. Pharmacopoeia for the practitioner insert and the containers of sodium chloride and water containing benzyl alcohol.

Caution must be used in attributing illness or death to benzyl alcohol in individual babies; many of the clinical features ascribed to benzyl alcohol toxicity are found in newborns seriously ill from other causes. The babies described with benzyl alcohol toxicity had serious underlying disease, but they also had biochemical evidence of benzyl alcohol toxicity.

FDA is involved in gathering more data on the problem, in cooperation with the Armed Forces Institute of Pathology, neonatologists, and the U.S. Centers for Disease Control (CDC).

Collaborative efforts with drug manufacturers, the American Society of Hospital Pharmacists, the American Academy of Pediatrics, the American Nursing Association, the U.S. Pharmacopoeial Convention, CDC[3], and others are under way to insure that the health care community is fully informed of the recent information.

Physicians can assist in this effort by using the form on the back of this *Drug Bulletin* to report any possible or definite cases of toxicity associated with benzyl alcohol.

References:

1. Brown WJ, Buist NRM, et al: Fatal benzyl alcohol poisoning in a neonatal intensive care unit (letter). *Lancet*, May 29, 1982; 1: 1250.
2. Gershanik JJ, et al: The gasping syndrome: benzyl alcohol (BA) poisoning? *Clin Res* 1981; 29: 895A.
3. *Morbidity and Mortality Weekly Report* 1982; 31: 290.

Hepatotoxic Potential of Ketoconazole Under Investigation

Three cases of fatal, massive hepatic necrosis, one case of nonfatal hepatitis and necrosis, and 20 cases of liver injury (usually with jaundice) have been reported in patients taking ketoconazole (Nizoral).

The drug is the only oral therapy approved for systemic fungal infections and is valuable for serious, systemic infections. (See November 1981 *Drug Bulletin.)*

Several cases of hepatitis were reported in the literature[1-3] just prior to and shortly after the drug's approval in June 1981. In these cases jaundice cleared and liver enzyme levels returned to normal after treatment was stopped or, in one case,[3] with continued ketoconazole treatment.

The three reported deaths occurred despite discontinuation of ketoconazole. The first occurred in a 67-year-old woman on ketoconazole therapy for 8 weeks. The second occurred in a 64-year-old man taking the drug for 28 days who had major surgery despite abnormal liver function and subsequently died of sepsis. The third case was a 22-year-old woman on ketoconazole therapy for 6 days. This patient was being treated for leukemia with drugs of known hepatotoxic potential.[4]

Although these cases were confounded by medical history and concomitant or preceding treatment with other drugs, the similar sequence and pattern of liver function abnormalities suggest that ketoconazole also played a role.

In the nonfatal case of hepatic necrosis, the 75-year-old female patient had been on ketoconazole therapy for 3 months with no concomitant medication.[4]

Manufacturer Sends Letter

Upon learning of the first case of fatal hepatitis that developed during ketoconazole therapy, the manufacturer, Janssen Pharmaceutica, sent a letter in March 1982 to prescribers informing them of the possibility of hepatotoxicity and alerting them to the consequent additions to the labeling.

The following was added to the Warnings section of the package insert for ketoconazole:

> Several cases of possible idiosyncratic hepatocellular dysfunction have been reported during NIZORAL treatment. It is important to recognize that liver disorders may occur with NIZORAL therapy. The rare occurrences of liver disorders could be potentially fatal unless properly recognized and managed. It is desirable to perform liver function tests, such as SGGT, alkaline-phosphatase, SGPT, SGOT and bilirubin, before treatment and at periodic intervals during treatment (monthly or more frequent), particularly in patients who will be on prolonged therapy or who have a history of liver disease. Instances of minor elevations of liver enzyme levels in patients on NIZORAL have been shown to normalize during therapy and may not necessitate discontinuation of treatment. However, if liver function tests are significantly elevated or other signs and symptoms are suggestive of hepatocellular dysfunction, ketoconazole should be discontinued.

The following has been added to the Precautions section:

> Information for Patient: Patient should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate bio-chemical testing can be done. Such signs and symptoms may include unusual fatigue, nausea or vomiting, jaundice, dark urine or pale stools.

Additional Cases

In addition to the four cases discussed previously, FDA has received reports of 20 additional cases of other liver injury, signs and symptoms of which included jaundice, elevated transaminases, bilirubin and alkaline phosphatase, anorexia, nausea, and/or

malaise. Duration of ketoconazole therapy in the affected patients ranged from 11 to 110 days with a mean duration of 56 days. Daily doses ranged from 100 mg to 400 mg with a mode of 200 mg daily.[4]

Tissue samples from the four cases of hepatic necrosis are currently under study.

Serious liver injury was not observed in clinical trials before the drug's approval for marketing in the United States, and became manifest only when large numbers of persons began taking the drug. (From June 1981 to May 1982 approximately 150,000 prescriptions for ketoconazole were written in the United States.)

FDA still feels that the benefit of the drug for certain serious fungal infections outweighs the risk of serious hepatic damage. However, physicians should monitor patients on ketoconazole as advised in the Warnings section of the labeling.

Practitioners may report any cases of liver dysfunction occurring with administration of ketoconazole by using the form on the back of this *Drug Bulletin*.

References:

1. Heiberg JK, Svejgaard E: Toxic hepatitis during ketoconazole treatment. *Brit Med J* 1981; 283:825.
2. McNair AL, Gascoigne E, et al: Hepatitis and ketoconazole therapy. *Brit Med J* 1981; 283: 1058.
3. Firebrace DAJ: Letter to the editor. *Brit Med J* 1981; 283: 1058-59.
4. ADR Highlight No. 82-6, FDA Division of Drug Experience, 5600 Fishers Lane, Rockville, Md. 20857.

Inappropriate Use of Smallpox Vaccine

Reports of adverse reactions to smallpox vaccination used to treat herpes infections are a source of concern for the medical community.[1-2]

One report concerned a patient with chronic lymphocytic leukemia who developed severe vaccinia necrosum after receiving smallpox vaccine in an attempt to treat recurrent herpes labialis. In 1981, the California Board of Medical Quality Assurance revoked the medical license of the physician involved but subsequently stayed the revocation and placed him on probation for 5 years.[3]

In general, smallpox vaccination is no longer necessary and it is ineffective for the treatment of any other disease. Moreover, its inappropriate use, especially in immuno-deficient patients, can result in unnecessary morbidity and mortality.

Following the worldwide eradication of smallpox, the World Health Organization amended the International Health Regulations, effective Jan. 1, 1982, to no longer require smallpox vaccination for international travelers.

The use of smallpox vaccine in civilians should be limited to personnel directly involved in work on smallpox or related viruses.

The Immunization Practices Advisory Committee of the Public Health Service, in its recommendations for the use of smallpox vaccine, states:

There is no evidence that smallpox vaccination has therapeutic value in the treatment of recurrent herpes simplex infection, warts, or any other disease. Smallpox vaccine should never be used therapeutically.

Smallpox vaccination of civilians is now indicated only for laboratory workers directly involved with smallpox or closely related orthopox viruses (e.g., monkeypox, vaccinia, and others).[4]

References:

1. *California Morbidity Weekly Report*, April 6, 1978.
2. *Morbidity and Mortality Weekly Report* 1979; 28:266.
3. *California Morbidity Weekly Report*, November 1981; 20:45.
4. *Morbidity and Mortality Weekly Report* 1980; 29:417.

Oral Medication for Cystic Acne

Isotretinoin (Accutane), also known as 13-*cis*-retinoic acid, has been approved for marketing for the treatment of severe cystic acne which is unresponsive to conventional therapy, including systemic antibiotics.

In many instances, the drug has been shown to result in complete and prolonged remission of cystic acne after only one course of therapy.[1-3] When a second course of therapy is needed, however, it should not be started until at least 8 weeks after the completion of the first course because patients may continue to improve after stopping the drug.

Adverse Reactions

Because of significant adverse reactions, 13-*cis*-retinoic acid should be reserved for patients with severe recalcitrant cystic acne. Adverse reactions are common, but in general are dose-related and reversible when therapy is discontinued.

In clinical studies, hypertriglyceridemia developed on treatment in 25 percent of patients, with about 10 percent of patients having an elevation of triglycerides above 500 mg percent. About 15 percent showed mild to moderate decrease in serum high density lipoprotein (HDL) levels, and about 7 percent had minimal elevations of serum cholesterol. Pretreatment and follow-up lipids should be obtained under fasting conditions and at least 36 hours after alcohol was last consumed. These tests should be performed weekly or biweekly until the lipid response to the drug is established. In the clinical studies, lipid abnormalities were reversible upon cessation of therapy.

The most frequent adverse reaction with this drug, cheilitis (lip inflammation), occurred in more than 90 percent of patients. Up to 80 percent of cystic acne patients in clinical tests experienced reactions relating to dryness of skin or mucous membranes.

About 40 percent developed conjunctivitis. About 16 percent developed musculoskeletal symptoms; these were generally mild to moderate and rarely required discontinuation of the drug. These symptoms cleared rapidly when the drug was stopped. Less than 10 percent of patients experienced rash or thinning of hair.

Approximately 5 percent experienced one or more of the following: peeling of palms and soles, skin infections,

nonspecific urogenital findings, nonspecific gastrointestinal symptoms, fatigue, headache, and increased susceptibility to sunburn.

Because teratogenicity was observed in animals, isotretinoin is contraindicated in patients who are pregnant or who intend to become pregnant. Because it is not known whether the drug is excreted in human milk, isotretinoin should not be given to nursing mothers.

It is also contraindicated in patients sensitive to parabens, which are used as preservatives in the formulation.

Patients should be advised against taking vitamin A and vitamin supplements containing vitamin A to avoid additive effects with 13-*cis*-retinoic acid.

Dosage should be individualized according to patient's body weight and severity of disease. Detailed prescribing information is contained in the practitioner insert available from Roche Laboratories, Nutley, N.J. 07110.

References:

1. Peck GL, Olsen TG, et al: Prolonged remissions of cystic and conglobate acne with 13-*cis*-retinoic acid. *N Eng J Med* 1979; 300: 329-333.
2. Farrell LN, Strauss JS, et al: The treatment of severe cystic acne with 13-*cis*-retinoic acid. Evaluation of sebum production and the clinical response in a multiple-dose trial. *J Am Acad Dermatol* 1980; 3: 602-611.
3. Jones H, Blanc D, et al: 13-*cis*-retinoic acid and acne. *Lancet* 1980; 2: 1048-1049.

Implantable Drug Pump

An implantable drug delivery system (INFUSAID) has been approved for patients who require the continuous administration of heparin or fluorouridine (FUDR).

Bacteriostatic water or saline may also be administered through the device with either drug to achieve the prescribed drug concentration. Water or saline is used to flush the reservoir and keep the catheter unobstructed during an interruption in drug therapy.

The device infuses heparin directly into the vena cava through a catheter, and is useful in treating patients with recurrent thrombophlebitis or pulmonary emboli who need chronic anticoagulation and who are refractory to other therapies.

The drug pump can also be used to infuse FUDR directly into the hepatic artery by catheter in patients with unresectable solid tumors of the liver or colon. Delivery of the drug directly into the hepatic artery facilitates a high concentration at the tumor site, while lowering the systemic level, possibly resulting in fewer toxic reactions to the drug.

Studies at the University of Michigan found the pump capable of delivering drug levels to the tumor up to 400 times greater than those possible through such other methods as intravenous infusion.

In heparin-treated patients, 92 percent of those in whom the device was used who had previously untreatable clotting problems were completely free of recurring disease during the period of the study.

This implantable drug delivery system is contraindicated in:

- Patients with severe psychiatric, emotional or neurological disturbances.
- Patients whose body size is not large enough to accommodate the bulk and weight of the pump.
- Patients who undergo frequent or long-term changes in altitude.
- Patients who engage in certain vigorous or rough occupations or activities; e.g., contact sports.

All contraindications related to long-term use of the drugs also apply.

Potential adverse effects of the pump involve device failure and loss of charging fluid. Device failure would change the amount of drug delivered and would require a corrective surgical procedure. (In experimental use in 137 patients for as long as 40 months, there were five pump failures, none of which caused serious complications.) Loss of charging fluid into the body might cause a toxic reaction.

Other potential complications include: cannula occlusion, wound infection, cannula dislodgement, skin necrosis, and immune thrombocytopenia associated with heparin.

The device is currently under study for dispensing drugs to treat brain tumors and for delivering insulin in the treatment of diabetes.

A complete description of the device and its use is available from the manufacturer, Infusaid Corp., 1075 Providence Highway, Sharon, Mass. 02067.

Approval of PUVA for Severe Psoriasis

PUVA, a treatment that uses the drug methoxsalen (8-methoxypsoralen, a psoralen derivative) in conjunction with ultraviolet A light for symptomatic control of severe psoriasis, has been approved by FDA. PUVA is recommended only for severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy.

Human Studies

To determine PUVA's long-term safety, FDA has monitored human studies since 1974 (see August-September 1978 *Drug Bulletin*) and has concluded that PUVA therapy is highly effective in treating severely debilitating cases of psoriasis not helped by other methods of treatment. PUVA is not a cure for psoriasis, however, as the symptoms and signs of psoriasis may disappear completely during the course of therapy, but may reappear without maintenance treatment.

More than 1,100 patients at 16 medical centers in the United States were involved in clinical trials with the following results:

- 88 percent of the patients were cleared of their symptoms.
- 3 percent failed to clear.
- 1 percent dropped out of the studies because of acute complications and 3 percent for other reasons.

Common acute side effects include nausea or itching, each in about 10 percent of patients. Transient, mild erythema is an expected reaction, but moderate or severe burns may occur. Safe use of PUVA requires careful patient monitoring.

Treatment with PUVA, although effective, carries with it a number of long-term risks, including premature aging of the skin and skin cancer. The treatment has been associated with a nine-fold increase in the risk of squamous cell carcinoma and a two-fold increase in risk of basal cell carcinoma. A

potential increased risk of cataracts is of concern but has not been documented in patients using proper eye protection.

Patients with hepatic insufficiency should receive PUVA therapy with caution because hepatic biotransformation is necessary for drug urinary excretion. Patients with cardiac disease or others who may be unable to tolerate heat stress should not be treated in a vertical UVA chamber.

The effects of PUVA therapy when administered to a pregnant or lactating woman are unknown. Therefore, caution should be exercised and treatment administered only if clearly needed.

The patient should be fully informed of the risks inherent in this therapy and should be given written information about it. Complete information for use, including leaflets for patients, can be obtained from the manufacturer of methoxsalen: Elder Pharmaceuticals, 705 E. Mulberry St., P.O. Box 31, Bryan, Ohio 43506. Pharmacists will be distributing patient leaflets when prescriptions are filled.

Course of Treatment

PUVA therapy is begun with the patient ingesting a prescribed dose of methoxsalen. Two hours later, after the drug has been absorbed and the skin sensitized to ultraviolet light, the patient is exposed to a measured amount of UVA light in a specially designed enclosure to complete the treatment.[1]

Treatments may be given as often as two or three times a week and may take 8 weeks or more for noticeable relief. Many patients must continue treatment indefinitely.

Patients should wear special highly-absorbing protective eyewear during the UVA treatment and 24 hours after taking methoxsalen to prevent cataract formation. An ophthalmologic examination is recommended prior to start of therapy, and yearly thereafter, because laboratory animals with unprotected eyes have developed cataracts in PUVA experiments.

Taking methoxsalen with meals is recommended to avoid nausea.

Reference:
1. *American Pharmacy*, Vol NS21, September 1981; 531(9): 34-36.

Erythromycin Estolate To Remain on Market

FDA has withdrawn a *Federal Register* proposal to remove erythromycin estolate from the market. The drug is sold under both the brand name, Ilosone, and the generic name.

This action is being taken by FDA after considering the recommendation of an ad hoc erythromycin estolate advisory committee. It recommended that the drug's clinical benefits outweigh its risk of increased hepatotoxicity and that it should remain available to be used at the physician's discretion.

Erythromycin estolate labeling has carried a warning of the drug's hepatotoxicity since 1962. A stronger boxed warning was added in 1973 (see January 1974 *Drug Bulletin*).

However, FDA initiated formal procedures to remove erythromycin estolate from the market in 1979, because of evidence of greater risk of hepatotoxicity in adults with the estolate than with other forms of erythromycin and disputed evidence of better bioavailability. (See November 1979 *Drug Bulletin*.)

When the ad hoc erythromycin estolate advisory committee convened in April 1981, it reviewed data from new bioavailability studies and adverse reaction reports. The advisory committee recommended that the estolate form of the drug should remain on the market, and the agency has accepted this recommendation.

The committee's advice was that data are insufficient to determine adequately the relative incidence or risk of hepatotoxicity in adults and that compared to the erythromycin base, when taken with food, initial serum levels with the estolate in adults are more reliable.

The advisory committee, however, suggested that physicians exercise clinical judgment in evaluating the risk/benefit ratio of the particular erythromycin formulation to be used in each individual patient since the incidence of hepatotoxicity for adults, but not for children, is greater for erythromycin estolate than for other erythromycins.

Class I Recalls

As a special service to health professionals, the *Drug Bulletin* is publishing information on recent Class I recalls. Class I recalls pose serious health hazards. The following products have been withdrawn voluntarily by the firms involved:

Heart Aid Cardiac Resuscitator, Model 60, serial numbers 26000 through 26335. The heart rate detection circuit is unreliable and double counts some wave forms. The device will deliver unintended defibrillating shocks, causing the patient to go into ventricular fibrillation. The manufacturer, Cardiac Resuscitator Corp., Lake Oswego, Ore., is recalling for modification of the electronics. Recall date: March 1982.

Bunn Model 65 Solid State Audio/Visual Alarm System for ventilators, serial numbers 0001 to 0180. The pressure alarm switch may not operate, thus failing to signal changes in ventilator pressure, resulting in hypoxic conditions. The manufacturer, Greene and Kellogg, Inc., Tonawanda, N.Y., is asking that all units be returned. Recall date: March 4, 1982.

Polycillin-N (Sterile Ampicillin Sodium) IM or IV injection, 500 mg (lots K1M55 & L1MO1), and 1 gram (lot L1MO2). The manufacturer, Bristol Laboratories, Syracuse, N.Y., is recalling for nonsterility. Recall date: March 9, 1982.

Normal serum albumin (human), 5 percent, Albuminar-5, lot V3109, 250-ml vials. Adverse reactions have been reported in debilitated patients. These included hypotension, arrhythmias, shaking chills, and respiratory insufficiency. The manufacturer, Armour Pharmaceutical Co., Kankakee, Ill., is recalling the identified lot. Recall date: Feb. 2, 1982.

Lifeline Endotracheal Tube, all lots. The cuffs may leak. When used as part of an emergency CPR kit for airway maintenance, it may be life-threatening because of the limited number of replacement tubes in the kit. The manufacturer, Life Line Products, Inc., Wheeling, Ill., is asking that the tubes be returned to their Prospect Heights, Ill., plant. Recall date: May 6, 1982.

Erratum

In the April 1982 *Drug Bulletin*, the dose of hepatitis B vaccine used in clinical trials should have read 20 or 40 *mcg*, not mg.

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ADDITIONAL INSTRUCTIONS FOR COMPLETING FORM FDA 1639

Use a separate report form for each case. Additional pages may be attached.

I. PATIENT/REACTION INFORMATION (ITEMS 1-12)

Items 2, 3, 4, 5. In case of a congenital malformation, record age, weight and height of the *mother*, and sex of the *baby*.

Item 8. Describe signs, symptoms and course of the drug related event.

Item 9. Indicate the status of the patient as of the reporting date and include discharge summary and/or autopsy findings, if available.

Item 10. Describe all diagnostic tests and exams results done as result of events in Item 8. Pertinent base line values and laboratory normals should be included.

Item 11. If "yes", describe treatment in Item 8.

Item 12. Hospitalization Required: If "yes", describe treatment in Item 8.

II. SUSPECT DRUG INFORMATION (ITEMS 13-20)

Item 13. Trade name and lot number, when available.

Item 14. As of date in Item 7. If drug(s) was given in a different dose or form previously, include dates and total daily dose for each drug exposure.

Item 15. As of the date in Item 7.

III. RECENT/CONCOMITANT DRUGS AND MEDICAL PROBLEMS (ITEMS 21-22)

Item 22. When reporting a congenital malformation, include date of mother's last menstrual period, gravidity, parity and previous abortions.

IV. OTHER INFORMATION (ITEMS 23-26)

Item 24. If this is a follow-up to a previous report, attach copy of initial report.

Item 25. (Record the name, title and address of the provider originating the report. THIS INFORMATION IS KEPT IN CONFIDENCE BY THE FDA AND IS NOT RELEASED UNDER THE FREEDOM OF INFORMATION ACT.)

After completing the form on the other side of this sheet, please tear off the page, triple fold, and staple or seal with tape. No postage is necessary.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MD 20857

FORM APPROVED: OMB 0910-0004.
Use of this form is prohibited after 12/31/85.

FDA CONTROL NO.

ACCESSION NO.

DRUG EXPERIENCE REPORT

I. REACTION INFORMATION

1. PATIENT ID/INITIALS (In Confidence)	2. AGE	3. SEX	4. WGT.	5. HT.	6. REPORTING DATE MO	DA	YR	7. REACTION ONSET DATE MO	DA	YR

8. DESCRIBE SUSPECTED REACTION(S)

9. OUTCOME OF REACTION TO DATE
- ☐ Alive with sequelae
- ☐ Recovered
- ☐ Still under treatment for reaction
- ☐ Died (Give cause/date)

10. TESTS/LABORATORY DATA CONFIRMING REACTION (Include biopsy and/or autopsy results)

11. WAS OUTPATIENT TREATMENT FOR REACTION REQUIRED? ☐ Yes ☐ No

12. WAS HOSPITAL TREATMENT FOR REACTION REQUIRED? ☐ Yes ☐ No

II. SUSPECT DRUG(S) INFORMATION

13. SUSPECT DRUG(S) - TRADE/GENERIC NAME(S), MANUFACTURER, IND/NDA NO.

14. TOTAL DAILY DOSE

15. ROUTE OF ADMINISTRATION

16. INDICATION(S) FOR USE

17. THERAPY DATES *(From/To)*

18. THERAPY DURATION

19a. WAS TREATMENT WITH SUSPECTED DRUG REDUCED IN DOSAGE? ☐ Yes ☐ No OR: ☐ Discontinued

19b. DID REACTION ABATE? ☐ Yes ☐ No

20a. WAS DRUG REINTRODUCED OR DOSE INCREASED? ☐ Yes ☐ No

20b. DID REACTION REAPPEAR? ☐ Yes ☐ No

III. RECENT/CONCOMITANT DRUGS AND MEDICAL PROBLEMS

21. OTHER DRUGS	TOTAL DAILY DOSE	ROUTE	DATES/DURATION OF ADMINISTRATION	INDICATIONS

22. DESCRIBE OTHER RELEVANT MEDICAL HISTORY (i.e., allergies, environmental or occupational exposure, previous drug reactions, pregnancy with gravidity/parity, ethnic origin.)

Your cooperation is needed to insure comprehensive, accurate, and timely use and interpretation of these data.

23. MFR NAME/ADDRESS

MFR CONTROL NO.

DATE SENT TO FDA

24. Check one
- ☐ Initial Report
- ☐ Follow-up Report

25. REPORTER'S NAME AND ADDRESS (In confidence)

NOTE: *Required of manufacturers by 21 CFR 310.300, 310.301 and 431.60. Manufacturers may attach additional clinical material and product analyses at their discretion.*

26. MAY THE SOURCE OF THIS REPORT BE RELEASED TO THE ARMED FORCES INSTITUTE OF PATHOLOGY? ☐ Yes ☐ No

☆U.S. GOVERNMENT PRINTING OFFICE 1982 361-176/103

12/3

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December 1982 Volume 12 Number 3

FDA Drug Bulletin

Chymopapain Approved
Human Insulin Receives FDA Approval
Tampon Packages Carry TSS Information
Proposal To Remove Phenacetin from Analgesics
Research on AIDS
Revision of Drug Approval Regulations Proposed
Reye Syndrome Awareness Program
Pregnancy Categories for Prescription Drugs
Final Recommendations Issued on Potassium Iodide
Topical PEG in Burn Ointments
Device and Lab Product Reporting
Class I Recalls

Chymopapain Approved

Chymopapain (Chymodiactin) intradiscal injection has been approved for the treatment of patients with documented herniated lumbar intervertebral discs whose signs and symptoms have not responded to conservative therapy over an adequate period of time.

Caution should be exercised when administering chymopapain, however, as anaphylactic reactions to the injection occur in about 1 percent of patients. Among the approximately 1,400 patients treated with the approved preparation, anaphylaxis has led to two fatalities, about 0.14 percent, a mortality rate similar to that of lumbar disc surgery.

In double-blind, randomized, placebo (saline)-controlled studies, chymopapain was effective when evaluated 6 weeks after injection in 44 of 55 patients (80 percent), while placebo was effective in 30 of 53 (57 percent), a statistically significant difference ($p = 0.008$).

The most frequently reported adverse effects were post-injection back pain and soreness (51 percent) and back spasm (29 percent). In addition to anaphylaxis, other less frequently reported adverse effects were: rash, itching, leg weakness and/or pain, leg cramping, headache, and urinary retention.

In the period immediately following injection, patients must be monitored closely for signs and symptoms of anaphylaxis, which can occur from within 1 minute to 20 minutes post-injection. Preliminary information indicates that risk of anaphylaxis may be greater in women, perhaps those with pretreatment erythrocyte sedimentation rates (ESRs) greater than 20 mm/hr.

Of a total of 909 patients in new drug application (NDA) clinical studies, nine cases of anaphylaxis were reported. Eight cases were in women, and five of them were in patients with pretreatment ESRs greater than 20 mm/hr. One patient died, despite intensive treatment. She had a pretreat-

HE 20.4003/3:

Information of Importance
To Physicians and
Other Health Professionals

FDA Drug Bulletin

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ment ESR greater than 20 mm/hr.

A second death was reported in a woman who suffered anaphylaxis after being injected with chymopapain. Despite intensive treatment, she died about 3 weeks after injection, reportedly of overwhelming pulmonary candidiasis.

Chymopapain has not been studied in the treatment of herniated discs in areas other than the lumbar spine.

The professional labeling states that the product is to be used only by physicians trained in chemonucleolysis. A training course in the use of chymopapain is available through a joint committee of the American Academy of Orthopedic Surgeons and the American Association of Neurological Surgeons.

Professional labeling is available from the manufacturer, Smith Laboratories, Northbrook, Ill.

Human Insulin Receives FDA Approval

Biosynthetic human insulin (Humulin), the first drug product developed through recombinant DNA techniques, has been approved by FDA for marketing.

Although representing a technological advance through demonstration of the scientific and commercial viability of recombinant DNA technology, biosynthetic human insulin (BHI) has not been demonstrated to offer clinical advantages over purified animal insulins. If patients are switched from one form of insulin to another, adjustment in dosage may be necessary.

BHI is derived from a special nondisease-forming laboratory strain of *Escherichia coli*. Thus far, no evidence of sensitivity to *E. coli* polypeptides or other substances has been demonstrated in clinical trials.

In 101 patients who had never before received insulin therapy, after 6 months of treatment with BHI there was no evidence of development of antibodies to *E. coli* polypeptides and no evidence of insulin allergy, lipodystrophy, or dermal hypersensitivity. However, antibodies to BHI were noted to develop.

In 112 patients transferred from animal insulins to BHI and treated for 3 months, one patient developed possible local insulin allergy; none developed lipoatrophy; and lipohypertrophy was uncommon. There was no evidence of development of dermal hypersensitivity to *E. coli* polypeptides.

Patients switched from animal insulins to BHI should be followed carefully during the first few weeks to determine whether dosage needs adjustment.

In clinical studies, an initial increase in mean fasting serum glucose levels was noted during the first month. During the second and third months of BHI therapy, mean serum glucose levels tended to decrease toward baseline values. However, as with switching patients from nonpurified to purified insulins (see November 1980 *Drug Bulletin*), some patients switched to BHI therapy may require higher dosages, some lower, and others no change at all. Because of the need for monitoring, patients should be cautioned not to switch insulins without consulting their physicians.

It is expected that Humulin will be available over-the-counter sometime in 1983, with its cost approximately 10

percent higher than purified insulin, according to the manufacturer, Eli Lilly and Co.

Tampon Packages Carry TSS Information

Tampon packages are required to carry information about Toxic Shock Syndrome (TSS) as of Dec. 20, 1982.

The precise wording of the information about TSS contained on the package or on the insert is not specified but must include the following information:

—Warning signs of TSS: e.g., sudden fever (usually 102° F or above) and vomiting, diarrhea, fainting or near fainting when standing up, dizziness, or a rash that looks like sunburn.

—What to do if these or other signs of TSS appear, including the need to remove the tampon at once and seek medical attention immediately.

—The risk of TSS to all women using tampons during the menstrual period, especially the reported higher risks to young women under 30, including teenage girls; the estimated incidence of TSS of 6 to 17 per 100,000 menstruating women and girls per year; and the risk of death from TSS.

—The advisability of using tampons with the minimum absorbency needed to control menstrual flow.

—Avoiding the risk of getting tampon-associated TSS by not using tampons, and possibly reducing the risk by alternating tampon use with sanitary napkin use during menstrual periods.

—The need to seek medical attention before using tampons again if TSS warning signs have occurred in the past or if women have any questions about TSS or tampon use.

If the information is contained in a package insert, the following alert statement must appear on the package label:

"**Attention:** Tampons are associated with Toxic Shock Syndrome (TSS). TSS is a rare but serious disease that may cause death. Read and save the enclosed information."

If the information is placed on the package itself, no separate alert statement will be required.

Any menstrual tampon dispensed from a vending machine is exempt from these requirements.

Background

TSS first came to the public's attention in 1980, when it was reported that the illness occurred most often in menstruating women using tampons. (See July 1980 *Drug Bulletin*.)

After an epidemiologic case-control study showed there was an increased risk of TSS in users of Rely brand tampons,[1] the manufacturer, Procter & Gamble, voluntarily withdrew Rely from the market in September 1980. (See November 1980 *Drug Bulletin*.) However, TSS continued to occur among users of other tampon brands.

As of Oct. 20, 1982, 1,869 TSS cases had been reported to the Centers for Disease Control. In 1981, 85 percent of reported TSS cases occurred in menstruating women, and 15 percent in males or females who were not menstruating when they became ill. The case fatality rate in 1981 was 3 percent. CDC continues to receive an average of 40 to 50 cases of TSS per month.[2]

IOM Report

Last June, the Institute of Medicine (IOM) of the National Academy of Sciences made public a report by its Committee on Toxic Shock Syndrome.[3]

The committee held a conference on TSS in November 1981. Conference papers are available as Part 2 of the June 1982 issue of *Annals of Internal Medicine*.

The IOM committee reviewed all available data, including a paper by Harvey et al.[4] questioning the association of TSS and tampon use. IOM concluded that: " . . . toxic shock syndrome, an illness that predominates in young, menstruating women using tampons, is associated with toxin-producing strains of *Staphylococcus aureus*, and [that] cases of the illness are still occurring."

As preventive steps, IOM recommended the following:

- Information about TSS and tampons should be made available so that women can make informed decisions about tampon use.
- Women who have already had TSS should be advised not to use tampons.
- Postpartum women should be informed that use of tampons may increase TSS risk.
- Women 15 to 24 years old should be advised that they are apparently at higher risk of TSS than older women.
- Women should be advised to minimize their use of high-absorbency tampons.
- Physicians and other health professionals should be informed about the variations in presentation of non-tampon-associated cases of TSS, should be alerted to the symptoms of TSS, and should be encouraged to report all

definite, probable, and suspected cases.

- Physicians should also be advised that treatment of TSS with beta-lactamase-resistant antibiotics apparently decreases the chance of recurrence.

Diagnosing Mild Cases

It has been demonstrated that two toxins, pyrogenic exotoxin C (PEC)[5,6] and staphylococcal enterotoxin F (SEF)[7,8] are associated with strains of *S. aureus* isolated from patients with TSS. It is not known whether these two toxins are actually the same toxin, or whether they are responsible for the signs and symptoms of TSS. No definitive diagnostic test for TSS is currently available.

Therefore, the CDC descriptive criteria must be used to define cases for epidemiologic purposes. Briefly, these criteria are: fever, rash, hypotension, involvement of at least three organ systems, and desquamation of the skin of the hands and feet 1 to 2 weeks after onset of illness. Orthostatic dizziness is now accepted as evidence of hypotension, and patients with *S. aureus* bacteremia can be included as cases. A "probable" case lacks one of these criteria. In all cases, evidence for another cause of the illness, if looked for, must be absent.

Clinicians are reminded that the CDC case definition does not require the presence of menstruation, tampons, or *S. aureus*.

It should also be noted that these diagnostic criteria are intended for epidemiological and reporting purposes, and are thus intentionally restrictive to minimize confusion of TSS with other diseases having similar signs and symptoms. However, it is possible that TSS manifests itself in a variety of ways and appears in mild forms as well as severe forms.

Physicians need to be aware that TSS cases may exhibit a spectrum of signs and symptoms of varying severity so that they can appropriately treat patients who show some, but not all, features of TSS and in whom other causes can be reasonably excluded.

Cases of TSS should be reported to the state health department, which will relay the information to CDC.

Treatment

As discussed in the November 1980 *Drug Bulletin*, patients with signs and symptoms of TSS should be told to immediately stop tampon use. TSS patients should be managed as those suffering from other forms of shock. Large volumes of fluid and supportive care should be used as needed. A vaginal examination should be performed with removal of any tampon. Cultures of vagina, cervix, blood, anterior nose, urine, and stool for *S. aureus* and other organisms should be obtained before initiating antibiotic therapy. There is no evidence that antibiotics are effective in treating active TSS cases. However, beta-lactamase-resistant antistaphylococcal antibiotics seem to be effective in preventing recurrences. The recurrence rate is approximately 30 percent. Women who have had TSS should be advised to discontinue tampon use at least until *S. aureus* has been eradicated from the vagina.

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Proposal To Remove Phenacetin from Analgesics

After considering the recommendations of two advisory committees and reviewing additional medical data, FDA has concluded that the risks of phenacetin in combination analgesics outweigh any benefits derived from its use. The agency has proposed to remove phenacetin from analgesic compounds because its chronic use or abuse can lead to kidney disease and premature death.

A *Federal Register* notice was published on Aug. 10, 1982, proposing to require manufacturers to delete phenacetin from combination analgesics and giving guidelines for reformulation of these products by Aug. 10, 1983.

History

Phenacetin has been widely used as an analgesic for more than 80 years. It has virtually always been used in combination with other analgesic ingredients, in this country or elsewhere. Thousands of cases of renal disease associated with use of phenacetin-containing products have been reported throughout the world, and various other countries have taken steps to restrict or prohibit the use of phenacetin.

A warning statement concerning the severe and irreversible toxic effects that can result from chronic and excessive use of phenacetin has been required in all products containing this ingredient since 1964.

In 1977, the FDA Advisory Review Panel on Over-the-Counter Internal Analgesic and Antirheumatic Products classified phenacetin as not safe for OTC use as an analgesic because of the high potential for abuse and for harm to the kidneys, and the possibility of hemolytic anemia and methemoglobinemia resulting from abuse.

The panel report stated that "In the opinion of the Panel, the evidence relating phenacetin to severe renal disease now derives from a world body of published reports so numerous and varied in design that the possibility of coincidental association is negligible and requires that phenacetin be removed from the OTC drug market."

The panel pointed out that retrospective case-control studies indicated that total doses of 2 to 4 kilograms phenacetin over a period of about 10 years would result in an increased risk of renal papillary necrosis.[1]

In 1978, FDA's Peripheral and Central Nervous System Drugs Advisory Committee evaluated data on the safety and effectiveness of phenacetin in prescription analgesic products.

The committee recommended that a statement on the association of phenacetin with renal damage should be required in the labeling of products containing phenacetin. At that time, FDA asked manufacturers to add a boxed warning to the professional labeling to highlight the association of large doses of phenacetin taken for long periods with severe kidney disease and with cancer of the kidneys.

FDA Review

FDA later reviewed additional medical data, some of which are cited at the end of this article.[2-6] (For additional references, see *Federal Register*, Tuesday, Aug. 10, 1982, pp. 34641-34642.) These data included the 1978 Bengtsson report,[3] in which more than 100 cases of renal carcinoma in users of phenacetin-containing analgesics were reported. In 1980, the first study of analgesic nephropathy and transitional cell carcinoma of the urinary tract was reported in the United States by Gonwa et al.[7]

Medical data reviewed by the agency showed that chronic use or abuse of phenacetin-containing products may lead to excessive ingestion, which could produce a clinical syndrome characterized by gastrointestinal symptoms with peptic ulcerations, anemia, hypertension, ischemic heart disease and, rarely, pigmentation, psychiatric disorders, and possible effects on pregnancy.[8] In some cases the syndrome includes serious kidney disease and ends in death.

Because other safe and equally effective analgesics are available and reformulation of phenacetin-containing products is possible, FDA does not feel the removal of phenacetin would deprive patients of essential analgesic products.

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Research on AIDS

FDA is working with other PHS agencies in several areas of research related to Acquired Immune Deficiency Syndrome (AIDS).

AIDS is a newly defined syndrome of high mortality and morbidity that has been seen since 1979 predominantly among homosexuals, intravenous drug abusers, Haitians, and persons with he-

mophilia A. The incidence of diagnosed AIDS is increasing markedly.

The cause of the immunosuppression is not known, but patients generally have evidence of defective cellular immunity, including lymphopenia and decreased ratios of helper to suppressor T-lymphocytes. Cutaneous anergy, decreased natural killer (NK) cells, and diminished proliferative responses to mitogens and specific antigens are also sometimes observed. Neutrophil function appears normal, and immunoglobulin levels are normal or elevated.[1]

Case Definition

The Centers for Disease Control define a case of AIDS as "a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause of diminished resistance to that disease." Such diseases include Kaposi's sarcoma (KS), *Pneumocystis carinii* pneumonia, and other "opportunistic" infections such as pneumonia, meningitis, or encephalitis due to one or more of the following: aspergillus, candida, cryptococcosis, cytomegalovirus, nocardia, strongyloides, toxoplasma, zygomycosis, or atypical mycobacteria; esophagitis due to candida, cytomegalovirus, or herpes simplex virus; progressive multifocal leukoencephalopathy; chronic enterocolitis (more than 4 weeks) due to cryptosporidiosis; or unusually extensive mucocutaneous herpes simplex of more than 5 weeks' duration.[2]

For epidemiologic purposes, CDC has established several exclusion criteria which include a patient's having received immunosuppressive therapy, such as corticosteroids, and a patient's having Hodgkin's disease or other lymphoma. CDC also will exclude, on a case-by-case basis, other patients with conditions that may predispose them to certain diseases seen in AIDS patients.

CDC received reports of 732 cases of AIDS (including 284 deaths) from June 1, 1981, to Nov. 12, 1982. Of the total cases, 73 percent occurred among homosexual or bisexual men, 4 percent among men of unknown sexual orientation, 6 percent among women, and 16 percent among heterosexual men. Of the total cases, 21 percent were among intravenous drug abusers, 6 percent were Haitians with no history of homosexual activity or intravenous drug abuse, and 0.8 percent were hemophiliacs.

Occurrence of AIDS among hemophiliacs has raised the question of whether the syndrome may be transmitted through blood products such as Factor VIII, as is hepatitis B and non-A-non-B hepatitis. FDA is investigating this hypothesis. There have been six cases of *Pneumocystis carinii* pneumonia with other opportunistic infections in hemophiliacs.

Analysis of cases of AIDS reported to CDC between June 1, 1981, and Nov. 12, 1982, shows that 50 percent had *Pneumocystis carinii* pneumonia without KS; 30 percent had KS without *Pneumocystis carinii* pneumonia; 7 percent had both *Pneumocystis carinii* pneumonia and KS; and 12 percent had other opportunistic infections. The mortality rate for cases of *Pneumocystis carinii* pneumonia without KS was 45 percent, and for KS without *Pneumocystis carinii* pneumonia, 20 percent. Cases with both *Pneumocystis carinii* pneumonia and KS had a mortality rate of 60 percent. Those with other opportunistic infections had a mortality rate of 47 percent. Cases have been reported from 32 states, with almost 80 percent concentrated in six metropolitan areas mainly on the east and west coasts of the country.[2]

Treatment

Treatment of patients with AIDS is challenging because they often have multiple opportunistic infections, and there are a limited number of drugs available to treat these ailments. Some suggestions concerning therapy, including an overview of commercially available drugs, were made at a recent conference of the American Society for Microbiology at the Memorial Sloan-Kettering Cancer Center.[3]

FDA is working to facilitate the availability of an Investigational New Drug Application (IND) to permit the New York City Health Department to store and distribute to qualified clinicians Ansamycin, a rifampicin derivative that is an investigational drug. Ansamycin is useful in treating infections caused by *Mycobacterium avium*, one of the opportunistic infections that has been seen in patients with AIDS. (*Mycobacterium avium* is an avian type of tuberculosis, commonly producing disease in chickens and swine but rarely in humans.)

FDA is also investigating whether the veterinary drug amprolium can be used safely in humans to treat cryptosporidiosis, a protozoan infection usually found in cattle, but which has been reported in persons with AIDS.

The agency is collaborating with CDC in studying serum samples from AIDS victims. In clinical studies of homosexual men with and without AIDS, government researchers have found ad-

ditional defects in cellular immunity to those described in the literature.[1-8]

Health professionals should be aware that AIDS may manifest itself in milder forms than specified in the case definition, and initial signs and symptoms may continue for months before a serious disease is apparent.[5]

Practitioners should consider the possibility of AIDS in patients with unexplained, chronic fever, weight loss, or generalized, persistent lymphadenopathy.

Health professionals should report all cases of confirmed or suspected AIDS to CDC through their local or state health departments. Even in cases in which there are uncertainties, such as when exclusion criteria are present, CDC would like to receive and screen the reports.

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Revision of Drug Approval Regulations Proposed

As part of its effort to improve the efficiency of the drug approval process while still maintaining a high level of public health protection, HHS has proposed to revise the regulations governing the approval of new drugs and antibiotics.

The intent of the proposal is to reduce the time it takes FDA to review drugs, to make FDA procedures less cumbersome, and to improve FDA's ability to evaluate promptly and thoroughly the safety and effectiveness of drugs.

As set forth in the *Federal Register* of Oct. 19, 1982, the following are some of the features of the proposed rule:

- Streamlined format for applications.
- Minimized supporting information with the remainder available upon FDA request.
- Fewer supplements to approved applications.
- Reduction of certain recordkeeping and reporting requirements on approved applications.
- Expediting hearing procedures on refusals to approve an application.
- Improved procedure for resolving scientific disputes.
- Clarification of policy on the acceptance and use of foreign data.
- New safety update reports for pending applications.
- Strengthening of the reporting system for adverse effects noted during postmarketing surveillance of approved drugs.
- Increased communications with applicants.

The streamlined format for applications would require a summary of the entire application and separate detailed sections to permit concurrent review by reviewers in each of FDA's reviewing disciplines—clinical, pharmacological, chemical, statistical, and biopharmaceutical.

The procedure for drug sponsors to update their pending new drug applications periodically would require that they supply FDA with information gleaned from ongoing investigational use of the drug or other sources, thus assuring that FDA reviewers have up-to-date safety data.

Modification of FDA's policy regarding the acceptance of foreign data would mean that approval of a new drug may be based solely on foreign clinical studies that meet U.S. testing standards, provided that delineated criteria are met, including that the study is applicable to the U.S. population.

To keep the adverse reaction reporting system current for marketed drugs,

manufacturers would have to report all adverse drug reactions within 30 days. The most serious reactions would have to be reported within 15 days, as they are now.

For more information about the proposal, contact: Michael C. McGrane, National Center for Drugs and Biologics (HFN-7), FDA, 5600 Fishers Lane, Rockville, Md. 20857; phone (301) 443-5220.

Reye Syndrome Awareness Program

A public awareness program about the association between salicylates, including aspirin, and Reye syndrome (RS) has been undertaken by FDA.

As part of this program, a letter signed by HHS Assistant Secretary for Health Edward N. Brandt Jr., M.D., along with a question-and-answer brochure, was sent to physicians and pharmacists. Practitioners can obtain 25 additional copies of the brochure upon request.

The program also included radio announcements, a feature article in *FDA Consumer* magazine, and a newspaper column by Surgeon General C. Everett Koop, M.D.

Additionally, FDA is making educational materials available to consumer and other organizations for distribution.

RS is characterized by vomiting and lethargy which may progress to delirium and coma in children who are recovering from viral infections, particularly influenza or chicken pox. The Centers for Disease Control estimates that about 600 to 1,200 cases occur each year in the United States. Death results in 20 to 30 percent of the cases, and permanent brain damage occurs in many other cases.

Earlier this year CDC reported on four studies (one each from Arizona and Ohio and two from Michigan) in which the use of salicylates and salicylate-containing drugs during an earlier viral illness was more common in patients who developed RS than in matched controls.[1]

An FDA working group audited some of the raw study data and performed an independent analysis of the data, as reported in the August 1982 issue of the *Drug Bulletin*.

This working group continues to reexamine existing data, to evaluate new data as it is submitted to the agency, and to aid in the development of new studies.

Among the new studies will be some initiated by the government. In November, Health and Human Services Secretary Richard S. Schweiker called for new research into the suspected Reye-salicylate association. The secretary directed the Public Health Service to make recommendations to him about new research "to help resolve a scientific dispute over the reported link" between the syndrome and aspirin-containing products. Secretary Schweiker's statement came shortly after the Executive Board of the American Academy of Pediatrics had issued a statement saying that it believed that a contraindication warning about RS in salicylate product labeling should be delayed. However, a subsequent statement of the academy urges that physicians use caution in recommending aspirin for the treatment of flu or chicken pox symptoms.

Although caution is being urged in recommending aspirin-containing products for children for symptomatic relief of influenza or varicella, aspirin and other salicylates remain medically valuable in children for other uses. For example, these products are preferred drug therapy for rheumatic fever and juvenile rheumatoid arthritis and are useful anti-inflammatory and antipyretic agents in various other illnesses.

Reference:

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Pregnancy Categories for Prescription Drugs

Labeling of some prescription drugs now includes information about their level of risk for the fetus and the extent of caution necessary in their use. FDA has established five categories (A,B,C, D, and X) to indicate a drug's potential for causing birth defects.

This new format was first announced in the September 1979 *Drug Bulletin*. Because of labeling revisions, many products now use this format. By November 1984 almost all prescription drugs will carry this information.

Briefly, the pregnancy categories have the following meanings:

A—Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote.

B—Animal studies do not indicate a risk to the fetus and there are no controlled human studies, *or* animal stud-

ies do show an adverse effect on the fetus but well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.

C—Studies have shown drug to have animal teratogenic or embryocidal effects, but there are no controlled studies in women, *or* no studies are available in either animals or women.

D—Positive evidence of human fetal risk exists, but benefits in certain situations (e.g., life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.

X—Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any possible benefit.

It should be noted that even if placed in the lowest risk category (Category A), a drug should not be used in pregnancy unless clearly needed.

In addition, labeling for drugs with a recognized use during labor or delivery, whether or not the use is stated in the *Indications* section of the labeling (e.g., analgesics), describes the available information about the effect of the drug on the mother and fetus.

For a more extensive discussion of the pregnancy categories and labor and delivery information, see the September 1979 *Drug Bulletin*.

Final Recommendations Issued on Potassium Iodide

FDA has issued final recommendations for use of potassium iodide for prevention of thyroid injury during a radiation emergency.

The recommendations were developed by the agency as a guideline for state and local health officials in deciding when to use the drug in radiation emergencies.

The recommendations suggest that state and local public health officials consider the use of potassium iodide in radiation emergencies for people who are likely to receive more than 25 rem to the thyroid gland from radioiodine released into the environment.

Potassium iodide for use in thyroid-blocking in a radiation emergency is a nonprescription drug, but it should be used only at the direction of a responsible public health official. The product must be dispensed with a patient information leaflet, which provides necessary information on how to use the drug safely and effectively.

The recommended daily dose of potassium iodide for adults and children over 1 year is 130 milligrams. Children under 1 year should receive 65 milligrams/day.

The agency concluded that during a radiation emergency the risks from short-term use of these relatively low doses of potassium iodide are outweighed by the risks of radioiodine-induced thyroid nodules or cancer (at a projected thyroid dose of 25 rem).

The recommendations are not binding; the decision of when and how to use potassium iodide, if at all, remains with state and local officials. It should be noted that the use of potassium iodide in a radiation emergency is not a panacea. It does not reduce the uptake or storage by the body of other radioactive materials, nor does it provide protection against external radiation. The recommendations stress that other protective measures such as shelter, evacuation, and respiratory protection also need to be considered.

A copy of the final recommendations and information on the product and its availability can be obtained from Bernard Shleien, Pharm. D., National Center for Devices and Radiological Health (HFX-4), 5600 Fishers Lane, Rockville, Md. 20857; phone (301) 443-6220.

Topical PEG in Burn Ointments

FDA cautions practitioners about the use of topical preparations containing polyethylene glycol (PEG) in burn patients with known or suspected renal impairment.

Researchers from the University of Virginia have reported renal destruction from PEG in animals[1] and renal failure in humans[2] treated with burn preparations containing PEG.

The syndrome observed by these researchers in rabbits and humans after application of a PEG-based antimicrobial cream resembles that seen following the ingestion of ethylene glycol and includes:

- Elevated total serum calcium
- Elevated serum osmolality
- Metabolic acidosis with large anion gap
- Renal failure

Nine cases of this syndrome have been reported over a 2-year period in patients treated at the University of Virginia with Furacin Soluble Dressing,

a PEG-based preparation. However, it is not clear to what extent deaths in patients with this clinical picture were related to the preparation. FDA has not received other similar reports of deaths associated with topical PEG, but absorption of other glycols from burn creams has previously been reported and shown to produce increases in serum osmolality.[3,4]

The following statement has been added to the professional labeling of Furacin Soluble Dressing:

"Furacin Soluble Dressing should be used with caution in patients with known or suspected renal impairment. The polyethylene glycol present in the base can be absorbed through denuded skin and may not be excreted normally by a compromised kidney. This may lead to symptoms of progressive renal impairment, such as increased BUN, anion gap, and metabolic acidosis."

References:

1. Herold DA, Rodeheaver GT, et al: Toxicity of topical polyethylene glycol. In press for *Toxicol and Appl Pharmacol.*
2. Bruns DE, Herold DA, et al: Polyethylene glycol intoxication in burn patients. *Burns* 1982; 9(1): 45-52.
3. Beckeris L et al: Propylene glycol as a cause of an elevated serum osmolality. *Am J Clin Pathol* 1979; 72: 633.
4. Kulick ML et al: Hyperosmolality in burn patients: analysis of an osmolal discrepancy. *J Trauma* 1980; 20: 223.

Medical Device and Laboratory Product Problem Reporting Program

FDA encourages health professionals to report problems with medical devices, including *in vitro* diagnostic devices, that represent a hazard to a patient or user or that relate to inadequate quality, safety, design, or performance. Some reportable problems are: injuries; incorrect, incomplete, misleading, or confusing labeling or instructions; design defects or designs that could lead to error in use of the product; packaging errors; or defective components.

FDA's Device Experience Network (DEN), located in the National Center for Devices and Radiological Health, began collecting data directly from health professionals in 1973 and has received nearly 17,000 reports. Because of these reports, significant changes and corrective actions have occurred. These include recalls, improvements in design or manufacturing procedures, replacement of components, and clarification of instructions (see November 1979 *Drug Bulletin*).

To report device problems, health professionals may:

- Call the 24-hour, toll-free telephone number (800) 638-6725 (in Maryland, call collect: (301) 881-0256 between 9 a.m. and 4:30 p.m.), or
- Mail the tear-out reporting form in this *Drug Bulletin*.

When reporting by telephone, provide: the name of the device; all available device identification (such as lot, serial, model, and product numbers); the manufacturer's name and address; your name, address, and telephone number; your employer or institution's name and address; and a description of the problems you observed or experienced.

Class I Recalls

As a special service to health professionals, the *Drug Bulletin* is publishing information on recent Class I recalls. Class I recalls pose serious health hazards. The following products have been withdrawn by the firms involved:

Heparin Sodium Injection USP, 1,000 USP units per ml, lot number 81275, 5-ml ampuls. Nonsterility was reported by a hospital laboratory and was confirmed by two contract laboratories. The manufacturer, Torigian Laboratories Inc., Queens Village, N.Y., recalled the product to the user level on Aug. 10, 1982.

Revital powder and gel, all codes. These products have been found to be contaminated with bacteria that have been associated with wound infection. Although labeled as both "medical devices" and "foods" the powder and gel have been offered for treatment of chronic wounds, skin ulcers, skin irritations, and other diseases. The products should be returned to the manufacturer, Robertson Resources Ltd., Wesley Drive, Salisbury, Md. Recall date: Oct. 27, 1982.

Product Problem Reporting Program
12601 Twinbrook Parkway
Rockville, MD 20852

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

BUSINESS REPLY MAIL
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Postage will be paid by addressee:

DR. JOSEPH G. VALENTINO
The U.S. Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, Maryland 20852

Medical Device & Laboratory Product Problem Reporting Program

What Is It?

An easy-to-use and nationally established program to report problems with medical devices and/or laboratory equipment used in health care. The program is funded by the Food and Drug Administration (FDA) and coordinated by the United States Pharmacopeia (USP).

What Kinds of Problems?

Anything is reportable that you consider to be a problem with the quality, performance, or safety of any device or piece of equipment used in medical care.

How Does It Work?

Reports may be submitted by completing the self-mailing form on the reverse side, or by calling the toll-free number indicated below. * USP forwards copies of these reports to FDA and the manufacturer for review and possible action. You may receive feedback from FDA and the manufacturer on your observations.

By request, USP can delete your name on the manufacturer's and/or FDA's copy.

Is It Effective?

Since its inception in 1973, the program has been successful in identifying and initiating many product design improvements and other corrective actions that have resulted from reports submitted by health care professionals.

CALL TOLL FREE ANYTIME

800-638-6725*

*In Maryland call collect (301) 881-0256 between 9:00 AM and 4:30 PM

REMEMBER TO USE ANY IN-HOUSE REPORTING PROCEDURES

After completing the form on the other side of this sheet, please tear off the page, triple fold, and staple or seal with tape. No postage is necessary.

Medical Device & Laboratory Product Problem Reporting Program

Form Approved: OMB No. 0910-0143

ACCESS

DATE

1. TRADE NAME AND TYPE OF PRODUCT (*Attach labeling if available*)

2. PRODUCT IDENTIFICATION
LOT NO. SERIAL NO. PRODUCT NO.

3. NAME AND ADDRESS OF MANUFACTURER

4. EXPIRATION DATE (*if applicable*)

5. YOUR NAME

6. YOUR FACILITY'S NAME, ADDRESS, ZIP CODE, AREA CODE AND PHONE NUMBER

7. PROBLEMS NOTED OR SUSPECTED

RETURN TO

United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852
Attn.: Dr. Joseph G. Valentino
Form FD 2519F (12/83)

OR

CALL TOLL FREE ANYTIME
800-638-6725*
in the continental U.S.
*In Maryland, call collect (301) 881-0256
between 9:00 AM and 4:30 PM